Technologies for Formulation and Delivery of Influenza Vaccines

Dexiang Chen

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PATH
A catalyst for global health

Presentation Overview

- Stability of current influenza vaccines.
- Formulation tools to improve the stability of influenza vaccine.
- Devices for intranasal delivery of live-attenuated influenza vaccine.

Challenges for Formulating Influenza Vaccine

- **Seasonal vaccines.**
  - Vaccine strains change every season; each strain may have different stability.
  - The tight production timeline leaves little time for formulation study each season.
  - Real-time and real-condition stability data are not available when the product is registered; stability data is collected while the product is in use.
  - Stability is often weighed unfavorably to other attributes, e.g., ease of use (prefilled syringes, liquid formulation of the live flu vaccine).

- **Pre-pandemic influenza vaccines (stockpiled).**
  - Short product shelf life resulted from applying the seasonal vaccine formulation.
  - Live vaccines do not have sufficient shelf life for stockpiling.
  - Shorter shelf life of vaccine compared to adjuvant led to separate stockpiles of bulk antigen and adjuvant. Blending and fill-finish will be required at the time of use– which will slow down the response to disease outbreak.

Typical Stability of Seasonal Influenza Vaccine and Recommended Storage

Current Influenza Vaccines	Stability	Recommended storage
Split/subunit influenza vaccines	• 12-18 months at 2° – 8°C • 4 weeks at 30°C	• Stored 2° – 8°C • Do not freeze • Protect from light
Live-attenuated influenza vaccines	• Liquid formulation: 18 weeks at 2° – 8°C • Lyophilized formulation: 12 months (?) at 2° – 8°C	• Store 2° – 8°C • Do not freeze

Issues Related to Inadequate Stability

- **Vaccine wastage due to expiration: monovalent H1N1 vaccine for the 2009/2010 season.**
  - US: 71 out of 162 million doses.
  - Australia: 9.7 out of 19 million doses.

- **Vaccine recall: monovalent H1N1 vaccine for the 2009/2010 season.**
  - 13 lots of live-attenuated H1N1 influenza.
  - One lot split H1N1 pediatric vaccine (800,000 doses).

- **Challenges for stockpiling pre-pandemic influenza vaccines.**
  - LAIV: cannot be stockpiled with current formulation.
  - Split/subunit vaccine: stockpile turnover and associated cost .

Factors Affecting Stability of the Influenza Vaccines

- Vaccine strain: e.g., heat stability of H1N1 virus.
- Production technology and processes: split/subunit/VLP, inactivation method, purification process, etc.
- Product characteristics: purity, contaminants, etc.
- Formulations and product presentation: stabilizers, liquid or freeze dried, and primary containers.

Considerations for Formulating Seasonal Influenza Vaccines

- **Subunit/split/inactivated/VLP influenza vaccines.**
  - Liquid formulation is preferred over lyophilized formulation for easy administration.
  - Prevention of aggregations and optimization of pH and stabilizers is a priority for achieving maximum stability.
  - Accelerated stability studies using novel analytical assays (e.g., biophysical assays) will likely facilitate formulation development.

- **Live-attenuated vaccines.**
  - Lyophilized formulation, although it requires reconstitution at the time of use, is less likely to have stability problem than the liquid formulation.
  - Optimization of lyophilization cycle is a priority because it will likely increase process yield and maximize stability.
  - Design a formulation that can withstand heat stress during storage and use.

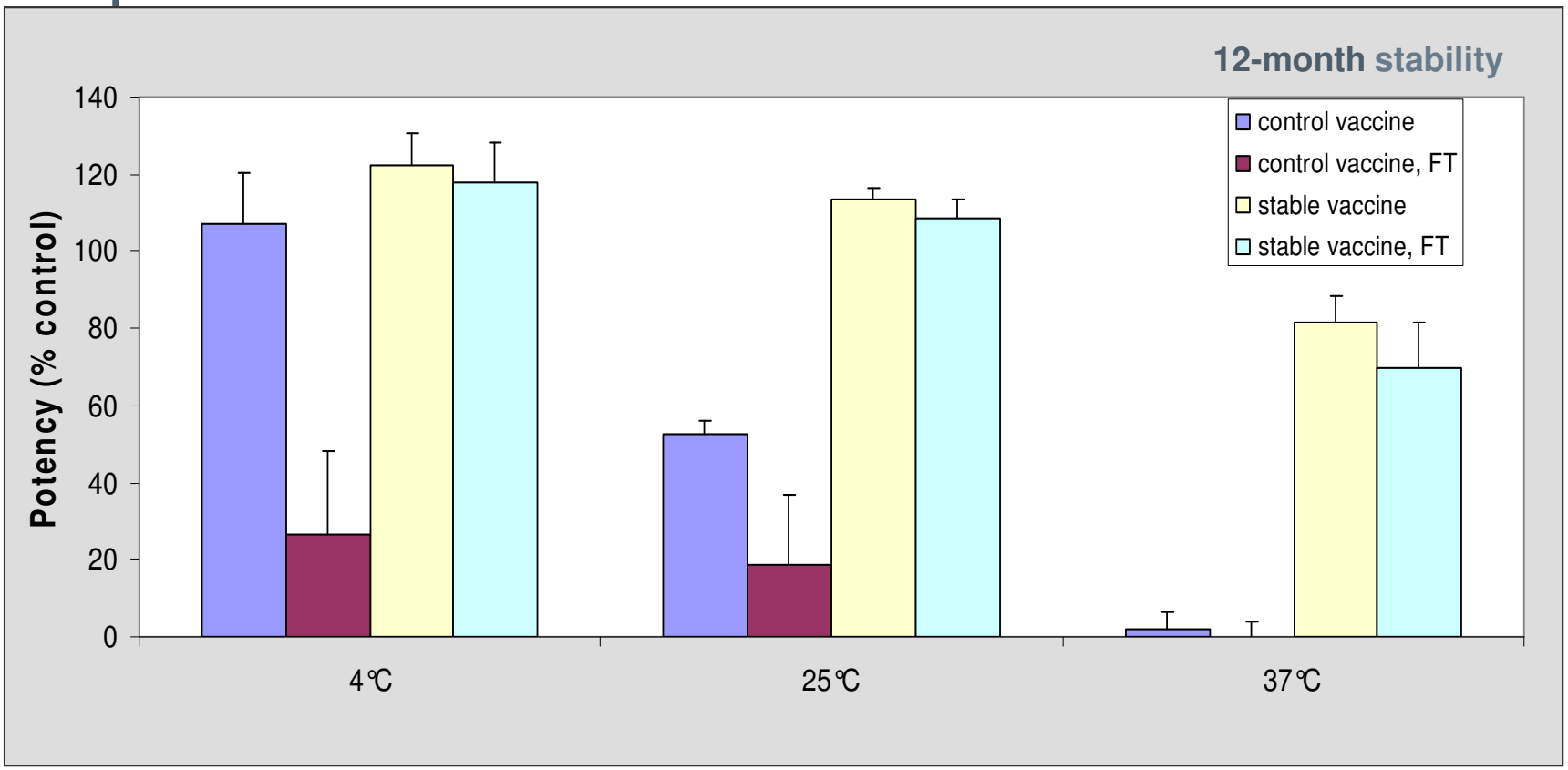
Considerations for Formulating Pre-Pandemic Influenza Vaccines for Stockpiling

- Both subunit and live attenuated vaccines should be considered.
- Long shelf life inside cold chain and short-term stability at ambient temperature is important
- Dry formulations usually have a longer shelf life.
- Novel formulation process may be considered (e.g., spray drying), particularly when the vaccine is stockpiled in bulk.

Technical Tools for Developing Liquid Formulations of Influenza Vaccine

- Apply technologies to address specific stability issues such as aggregation, oxidation, and freeze sensitivity.
- Computational analysis of protein structure to inform formulation design.
- Biophysical assays to facilitate formulation development, e.g., high throughput protein structural assays.
- Use of statistical tools (e.g. Design of Experiment) to study the interactions of the formulation variables.

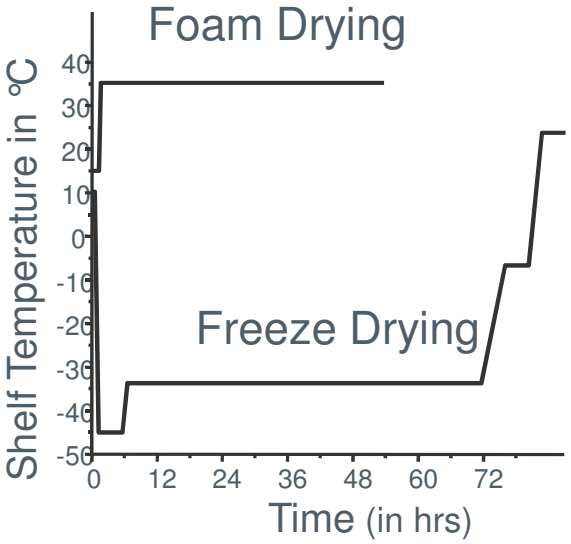
Example #1: Stable Liquid Formulation of Hepatitis B Vaccine



Control vaccine formulation: saline, pH 6.8
Stable vaccine formulation: histidine phosphate buffer, propylene glycol, pH 5.5

FT = Three cycles of freezing (-20℃, 24 hrs) and thawing (24℃, 4 hrs)

Example #2: Novel Processing Technologies- Foam Drying



Time to 1 log TCID50 loss live influenza virus vaccine

	Foam Dried	Lyophilized
Process loss	-0.2 ± 0.1 log	-0.2 ± 0.1 log
Stability @25 °C*	26.3 ± 6.9 mo	1.6 ± 0.6 mo
Stability @37 °C	4.8 ± 3.0 mo	0.6 ± 0.1 mo

Courtesy of Dr. Vu Truong, Aridis Pharmaceuticals

Effort Underway to Apply These Technologies to Stabilize Influenza Vaccines-Opportunity to Collaborate

Technology	Subunit Vaccine	Live Attenuated Vaccine
Liquid formulation	X	X
Foam drying		X
Spray drying	X	X
Freeze drying	X	X

BARDA funded a 3-year project for PATH to develop stable formulations of subunit and LAIV vaccines with extended shelf life.

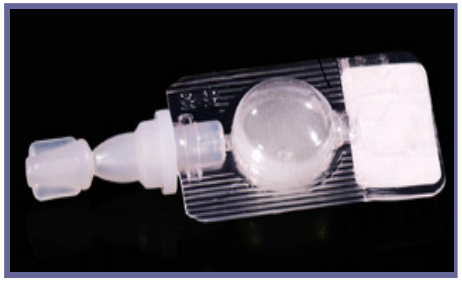
Device Options for Intranasal Delivery of Live-attenuated Influenza Vaccine

Types of Nasal Delivery Devices

	Drops		Liquid Spray			Powder
	Not prefilled	Prefilled	Not prefilled	Prefilled	Auto-recon devices	Powder delivery
Single use	Tuberculin syringe OPV dropper	Blow-fill-seal vials Uniject dropper	Wolfe-Tory MAD Nasal SIIL device Lindal device	BD AccuSpray Aptar bi-dose Mystic Versidoser	BD auto-recon IN device Mystic VRX2	Direct Haler BD dry powder inhaler Aptar bi-dose
Multi-use			Aptar multi-dose Rexam Advancia Wolfe-Tory MADomizer	OptiNose liquid AerovectRx Aerovax		OptiNose powder

Potential Devices: Prefilled Droppers

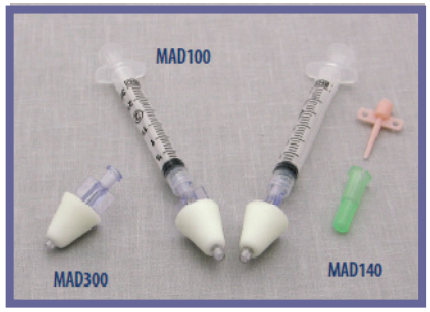
Blow-fill-seal (BFS) devices



Uniject® DP dropper

Advantages	Disadvantages
• Simple low-cost devices. •BFS technology should allow rapid sterile filling of devices. •Design and development work for Uniject® DP (dropper) has been completed by BD. •Uniject® DP expected to be simpler/less-expensive than Uniject® with needle.	• Requires liquid formulations. • Drops might be slower to administer than sprays.

Potential Devices: Single-Use Liquid Sprayers

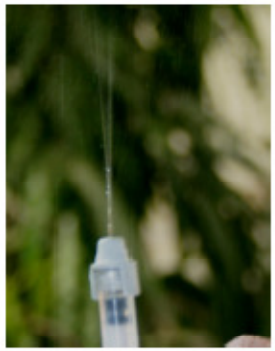


Advantages	Disadvantages
• Simple low-cost devices. • "Mimic" delivery by AccuSpray. • Compatible with lyophilized and liquid formulations.	• Generation of spray requires plunger to be pushed "hard". • Particles can block spray nozzle. • Dead space 70-100 ul. • Largest number of steps per dose.

User Dependence of Device Performance

Administration of vaccine

Caution! The person administering the vaccine should be trained to push the plunger of the syringe in a single firm and quick push to ensure that the delivered liquid give the best spray. A slow delivery will result in a more concentrated spray. The photos below show improving spray plumes with increasing plunger force



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Maximum force

Thank you

Contact Information

Formulation technologies:

Dexiang Chen, dchen@path.org

Delivery technologies:

Darin Zehrung, dzehrung@path.org

Nasal device landscape analysis report

Kathy Neuzil, kneuzil@path.org